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Creatine Phosphokinase-MB (CPK-MB) and the Diagnosis of Myocardial Infarction

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Creatine phosphokinase-MB (CPK-MB) is the most sensitive and the most specific indicator available for the diagnosis of an acute myocardial infarction. With the exception of after-cardiac surgical procedures, the degree and the duration of CPK-MB elevation in serum approximates the extent of an acute myocardial infarction, although a variety of factors may affect the reliability of such an index. Differences in the fractionation and assay methods for the creatine phosphokinase isoenzymes have produced conflicting documentation as to the presence of CPK-MB in tissues other than myocardium and the release of CPK-MB under conditions other than an acute myocardial infarction. The embryological development of the CPK-MB isoenzymes, as well as the various conditions involving increased CPK-BB serum activity, also deserve attention.

THE DIAGNOSIS of myocardial infarction (MI) has been classically based on a history of chest pain plus electrocardiographic (ECG) documentation of new Q-waves and evolving ST-T wave changes. Misdiagnosis is known to occur, for some patients either describe atypical symptoms or suffer a so-called "silent MI."[1,2] Moreover, a significant number of false-positive[3] and false-negative[4] results have been reported on ECG. Even clinical correlation with autopsy findings may produce biased results, since some 6 to 12 hours may be required after the onset of chest pain before the distinctive changes of myocardial necrosis can be detected at postmortem examination. As a result, clinical laboratories have become increasingly relied upon either to establish or to rule out the diagnosis of acute myocardial infarction. Since Wroblewski and co-workers first reported the association of elevated serum glutamic oxaloacetic transaminase (SGOT) activity with the occurrence of an acute MI,[5] a number of enzymes have been found to exhibit increased serum levels during the course of an acute MI. The enzymes, SGOT, lactic dehydrogenase (LDH), and creatine phosphokinase (CPK), are measured most frequently, but they are present in a variety of tissues and are released into serum under a variety of circumstances other than myocardial infarction.[6,7] The search for specific myocardial markers has led to improved techniques for the quantitative analysis of the isoenzymes of LDH and CPK. Despite great enthusiasm for the isoenzyme CPK-MB as a diagnostic indicator of myocardial infarction, the current medical literature contains conflicting reports as to whether: (1) CPK-MB is present only in myocardium, (2) CPK-MB is released only with myocardial infarction and (3) the degree and duration of CPK-MB elevation in serum reflects the extent of myocardial infarction.

Some of the discrepancies in the reports of CPK-MB activity arise from pronounced differences in either fractionation or assay techniques. At least three CPK isoenzymes, MM, MB and BB, have been separated either by electrophoresis or

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CCU = coronary care unit
CPK = creatine phosphokinase
ECG = electrocardiogram (electrocardiographic)
LDH = lactic dehydrogenase
MI = myocardial infarction
NADPH = dihydronicotinamide adenine dinucleotide phosphate
SGOT = serum glutamic oxaloacetic transaminase

column chromatography (see Figure 1). Other minor bands of CPK activity,[8-12] including a mitochondrial enzyme,[13,14] have been identified, but their clinical significance remains obscure. Assay of CPK activity usually is conducted by using a coupled enzyme system, involving hexokinase and glucose-6-phosphate dehydrogenase, and linking the production of adenosine triphosphate (ATP) in the reverse CPK reaction to the ultimate formation of dihydronicotinamide adenine dinucleotide phosphate (NADPH) (see Figure 2). The NADPH is then measured by spectrophotometry or fluorometry, or by the formation of an insoluble dye, such as formazan. The CPK isoenzymes readily lose their activity unless some thiol compound is added to the assay media.[15] Moreover, a number of anions reversibly inactivate CPK-BB[18] and heat can irreversibly inactivate all the CPK isoenzymes.[19] Dilution of serum samples can result in enhanced CPK activity, although the ratio of activities for the CPK isoenzymes remains constant.[20] Thus the final reported activities for the CPK isoenzymes separated either by electrophoresis or column chromatography may differ depending not only on the temperature, pH or buffer employed, but also on the nature and concentration of thiol reagent used, the penetration of the coupled indicator enzymes into the support gels, or the extent of isoenzyme elution from the support gels.[6,21,22] An assay method based on the differential thiol activation of CPK-MM and CPK-MB by glutathione and dithiothreitol has been reported,[23,24] but subsequent workers have found it to be unreliable.[25-30] Also, an immunological technique, utilizing antibodies to either the M- or B-subunit of CPK, has been applied quantitatively in a research setting,[31] but its routine clinical utility remains to be established.

The CPK isoenzymes MM, MB and BB are present primarily in the cytosol,[32] but have also been reported associated with the myofibrillar apparatus of muscle cells.[33,34] Embryologically, CPK is initially present in the BB-form in all tissues.[12,33,35] In developing skeletal muscle, MB and then MM gradually appear in association with the development of myofibril contractile elements.[33,35,36] In the adult skeletal muscle, MM has been reported by some workers to be the only CPK isoenzyme present,[37-46,52] but numerous other workers report up to 4 percent of total CPK activity to be present as CPK-MB.[33,35,47-49] In brain, on the other hand, CPK-BB remains the predominant isoenzyme throughout embryological development and into adult life.[33,35] For myocardium, the embryological isoenzyme development is similar to that of skeletal muscle, except that in an adult approximately 20 to 30 percent of the total CPK activity has been reported to be CPK-MB.[31,33,35,41-43] An exception to this is the predominance of the BB-isoenzyme in the myocardium of chickens and some other avian species.[50,51]

As mentioned above, conflicting reports have appeared as to whether CPK-MB is present in human skeletal muscle. Other tissues reported to

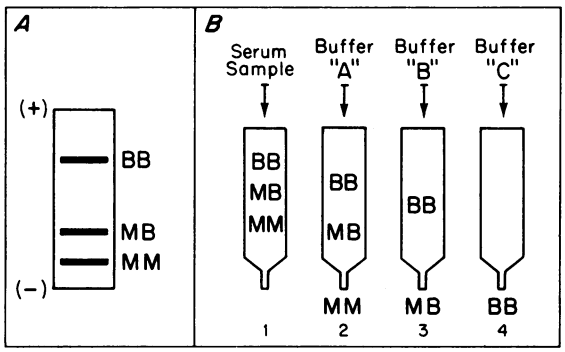

Figure 1.—Fractionation Methods. Showing fractionation of serum CPK into isoenzyme components by **A**, electrophoresis and **B**, DEAE-Sephadex column chromatography.

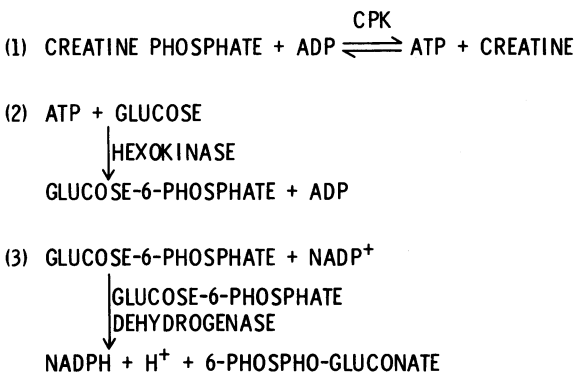

Figure 2.—Assay Method. Showing coupling of reverse CPK reaction **1**, with hexokinase **2**, and glucose-6-phosphate dehydrogenase **3**, mediated reactions to yield NADPH as product assayed.

contain CPK-MB include tongue, diaphragm and aorta—all of which contain CPK-MM as the predominant isoenzyme.[31,49] Also prostate, uterus, pancreas, intestine, bladder and stomach are reported to contain CPK-MB, but predominantly CPK-BB.[31,53] Lung, kidney, thyroid and adrenal have been reported to contain CPK-BB, but with either CPK-MM or CPK-BB predominating.[31,43,49,52,53] Liver has been found to contain low levels of CPK-BB.[49,52-54] In sharp contrast to the above results, Sobel and collaborators[38] and Galen and Gambino[43] surveyed a variety of human tissues obtained at surgery and were able to identify CPK-MB only in myocardium. Such conflicting results may derive from differences in extraction, fractionation and assay conditions as employed in the various laboratories. Therefore, although CPK-MB appears to be present in tissues other than myocardium, further research will be required to resolve this issue.

CPK-MB has been found to be both very specific and very sensitive for an acute MI. Usually, some four to six hours are required following the onset of the chest pain before CPK-MB becomes elevated in the serum of patients suffering an acute MI.[21,43,45,55,59] The peak of CPK-MB activity is usually observed within 12 to 24 hours, and then returns to normal levels within 24 to 48 hours, some 24 hours or so before total CPK activity returns to baseline levels. An incidence of up to 6 percent false positives[56] and up to 6 percent false negatives[57] have been reported for CPK-MB in the diagnosis of acute MI. Depending upon the methods employed, normal values for CPK-MB range from 0 to 3 percent of the total serum CPK activity. Compared to CPK-MB, LDH-isoenzymes have a reported incidence of 5 percent false-negatives and 14 percent false-positives in the course of an acute MI.[56] Reliance upon total LDH, CPK or SGOT results in even higher numbers of false positives[43,59-62]—further indication of nonspecificity in the diagnosis of an acute MI.

Although CPK-MB is of great value in a coronary care unit (CCU) setting, it is of lesser utility following cardiac surgical procedures. For procedures involving coronary bypass grafting, valve replacement or repair of congenital defects, CPK-MB is usually elevated postoperatively. The release of CPK-MB occurs intraoperatively, and by 18 hours after operation the CPK-MB has been reported back to normal levels in 74 percent of cases.[63,64] Neither the level of CPK-MB activity, nor the total CPK activity reliably indicates the occurrence of an acute MI in the perioperative period for cardiac surgical procedures.[63,65] Similar conclusions have been reported previously for LDH, SGOT and total CPK[66,67] although a recent study found a good correlation for LDH isoenzymes,[68] despite the fact that hemolysis can produce the same LDH isoenzyme profile in the absence of an acute MI. The highest levels of CPK-MB tend to occur with aortic valve replacement.[65] The contributing effects of hypothermia, fibrillation, defibrillation and post-pump sequelae following cardiac operations can only be speculated upon at present.[69] Establishing the diagnosis of an acute MI after a cardiac operation involves documenting appropriate ECG changes, but the appearance of Q-waves postoperatively may merely reflect an old MI and not the occurrence of an acute MI.[70,71] Myocardial scans have been reported to correlate with the occurrence of an acute MI, but again both false positives and false negatives are known to occur.[69,72-74]

CPK-MB release has also been reported to occur in a variety of circumstances in the absence of an acute MI, including the following: tachyarrhythmias,[22,75] atrial fibrillation,[22,75-77] cardioversion,[22,78] cardiopulmonary resuscitation,[78] cardiac catheterization,[43] multiple trauma,[43] dermatomyositis,[47] polymyositis,[35,41,47] viral myositis,[47] muscular dystrophy,[35,43,79] myoglobinuria,[43] coronary insufficiency,[61,76] angina pectoris,[61,76] congestive heart failure,[61,76] pulmonary embolism,[61,76] malignant hyperthermia,[43,80] hypothyroidism[44,81] and carbon monoxide poisoning.[80] Such documentation contrasts with numerous other reports of failure to detect elevated serum CPK-MB activity: despite a total CPK activity of 80,000 units per liter in acute rhabdomyolysis;[82] following a variety of thoracic, abdominal, genitourinary or orthopedic surgical procedures;[38,39] cardioversion;[83] cardiac catheterization;[38,55] pulmonary embolism;[83] convulsions;[77] angina pectoris;[83] trauma,[42] or hypothyroidism.[77,84] Sax and co-workers have reported on a series of 14 patients having elevated CPK-MB of 6 to 62 percent of the total CPK activity, despite normal or mildly elevated levels of total serum CPK activity.[11]

Although the concentration of CPK-BB is often reported along with CPK-MB, until recently CPK-BB has rarely been detected in serum. Efforts to prevent irreversible inactivation of CPK-BB activity have resulted in recent reports of elevated CPK-BB activity in patients with chronic renal failure,[85] gastric cancer[86] and malignant hyperthermia.[87]

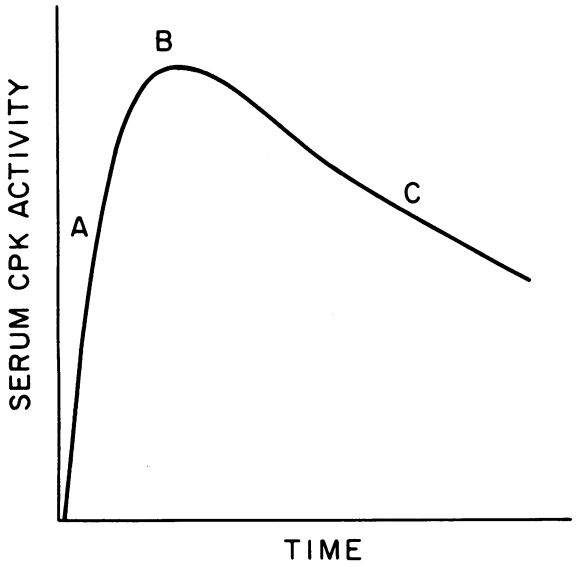

Figure 3.—CPK Kinetics. Showing release phase into **A,** serum; **B,** peak measured activity, and **C,** disappearance of CPK from serum. The slope of the disappearance segment has been used to calculate infarct size.

Itano has also reported increased serum CPK-BB in a series of 16 patients with conditions involving chronic lymphocytic leukemia, congestive heart failure and obstructive lung disease, fatal enterocolitis, syncope and cardiopulmonary resuscitation.[88] Conflicting reports have appeared relating elevated CPK-BB activity in serum with acute brain injury and central nervous system surgical procedures.[89-92]

Conclusions relating the degree and duration of serum CPK-MB elevation to the extent of myocardial infarction have been based on experimental protocols in animals.[54,93-96] Following the onset of an acute MI, the kinetics of both CPK release into serum from the area of infarction and subsequent CPK disappearance from serum can be shown by a plot of serial determinations of serum CPK activity as a function of time (see Figure 3). Estimates of infarct size in CPK-gram equivalents can then be derived from computer-assisted calculations based on the fractional disappearance rate of CPK from serum.[94] In such calculations, CPK-MB is assumed to be present only in myocardium. Furthermore, the size of the infarct, the rate of CPK-MB release, the rate of local CPK-MB inactivation and catabolism, and the disappearance rate of CPK-MB from serum, have all been assumed to be constant measures. The possible effect of variations in myocardial perfusion or reperfusion has been assumed to be negligible. Extracellular volume changes have likewise been considered insignificant. Although only 30 percent of the total CPK activity expected to be released from an area of infarction could be accounted for by the total amount of CPK activity detected in the serum of the experimental animals, the figure of 30 percent has also been considered a constant, and even applied to human studies.[97,98] In more recent work this figure is reported to be 15 percent[96,99] The reticuloendothelial system has been shown responsible for the disappearance of CPK activity from serum, with neither renal nor hepatic disease appreciably affecting the rate of CPK clearance.[6] Unresolved factors regarding CPK-MB and the extent of an acute MI include the reversibility of ischemic changes, including enzyme release,[100,101] the lack of precision in morphological estimates of infarct size,[93] the observation of diminished CPK activity in normal-appearing myocardial tissue bordering an infarction[94,101] and the role of reversible inhibition of CPK activity in areas of ischemia.[102] Therefore, except after cardiac surgical procedures, the degree and duration of CPK-MB elevation in serum can be used to approximate the extent of an acute MI, but a variety of factors may affect the reliability of such an index.[102,104]

The utilization of CPK-MB values in the diagnostic decision process requires a comparison with so-called normal values.[105] Significant differences in reported normal values for CPK-MB have been obtained from different analytical methods. Moreover, such normal values have usually been derived from populations of either healthy laboratory technicians or medical students, or from populations of hospital patients without cardiovascular disease. Perhaps a more appropriate reference population would include patients of similar age, sex, activity, medication usage and co-morbid diseases, but without evidence of an acute MI.

Despite the conflicting reports encountered during the survey of the current CPK-MB literature, the following conclusions have been reached: (1) CPK-MB appears to be present in tissues other than myocardium, including skeletal muscle, (2) CPK-MB appears to be released into serum under conditions other than myocardial infarction and (3) the degree and duration of CPK-MB elevation in serum is only an approximation, and not a reliable indicator of the extent of myocardial infarction.

CPK-MB appears to be the most sensitive and the most specific indicator of an acute MI availa-

ble, but astute clinical judgment is still required to reach the most reliable diagnostic decision and thereby to provide the most appropriate basis for subsequent management. Since CPK-MB may be released in conditions involving reversible myocardial injury, such as ischemia, congestive failure or tachyarrhythmias, other diagnostic criteria besides CPK-MB elevation alone would appear warranted to establish the diagnosis of an acute MI reliably. Unless serum analysis for CPK-MB is carried out within 12 to 24 hours after the onset of chest pain, false-negative results may ensue. The greatest predictive value of CPK-MB for an acute MI will be in the CCU setting, where the prevalence of acute MI is the highest.[106] The diagnosis of acute MI following cardiac surgical procedures will continue to be difficult because in most patients there appear to be elevated CPK-MB levels in the early postoperative period as a result of surgical trauma to myocardial tissue. Although myocardial scans may eventually contribute reliable, independent information relative to the diagnosis of an acute MI, further refinements will be required for this relatively expensive procedure before routine clinical use can be justified as reasonably cost-effective.

REFERENCES

1. Kannel WB, Feinleib M: Natural history of angina pectoris in the Framingham study. Am J Cardiol 29:154-163, Feb 1972
2. Margolis JR, Kannel WB, Feinleib M, et al: Clinical features of unrecognized myocardial infarction—silent and symptomatic, eighteen year follow-up: The Framingham study. Am J Cardiol 32:1-7 Jul 1973
3. Goldberger AL: Myocardial Infarction—Electrocardiographic Differential Diagnosis. St. Louis, CV Mosby, 1975
4. Johnson WJ, Achor RWP, Burchell HB, et al: Unrecognized myocardial infarction—A clinicopathologic study. Arch Intern Med 103:253-261, Feb 1959
5. La Due JS, Wroblewski F, Karman A: Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science 120:497-499, Sep 24, 1954
6. Sobel BE, Shell WE: Diagnostic and prognostic value of serum enzyme changes in patients with acute myocardial infarction, *In* Yu P, Goodwin JF (Eds): Progress in Cardiology, Vol. 4. Philadelphia, Lea and Febiger, 1975, pp 165-198
7. Batsakis JG, Preston JA, Briere RO, et al: Iatrogenic aberrations of serum enzyme activity. Clin Biochem 2:125-133, Dec 1968
8. Madsen A: Creatine phosphokinase isoenzymes in human tissue with special reference to brain extract. Clin Chim Acta 36: 17-25, Jan 1972
9. Velletri K, Griffiiths WG, Diamond I: Abnormal electrophoretic mobility of a creatine kinase MM isoenzyme. Clin Chem 21:1837-1838, Nov 1975
10. Hooten BT: Creatine kinase isoenzymes and the role of thiol groups in the enzymic mechanism. Biochemistry 7:2063-2071, Jun 1968
11. Sax SM, Moore JJ, Giegel JL, et al: Atypical increase in serum creatine kinase activity in hospital patients. Clin Chem 22:87-91, Jan 1976
12. Watts DC: Creatine kinase-(adenosine 5'-triphosphate-creatine phosphotransferase). *In* Boyer PD (Ed): The Enzymes, Vol VIII A. New York, Academic Press, 1975, pp 384-456
13. Jacobus WE: Heart creatine kinase—Heterogeneous composition of the mammalian MB-isoenzyme. J Mol Cell Cardiol 7:783-791, Oct 1975
14. Sobel BE, Shell WE, Klein MS: An isoenzyme of creatine phosphokinase associated with rabbit heart mitochondria. J Mol Cell Card 5:367-380, Aug 1972
15. Wong PCP, Smith AF: Biochemical differences between the MB and MM isoenzymes of creatine kinase, Clin Chim Acta 68:147-158, Apr 15, 1976
16. Milner-White EJ, Watts DC: Inhibition of adenosine 5'-triphosphate-creatine phosphotransferase by substrate anion complexes. Biochemistry J 122:727-740, May 1971
17. Warren WA: Identification of creatine kinase inhibitor in human serum. Clin Biochem 8:247-253, Aug 1975
18. Nealon DA, Henderson AR: Lability of human creatine kinase isoenzymes at 37° C—A complication of electrophoretic separation. J Clin Path 28:834-836, Oct 1975
19. Morin LG: Improved separation of creatine kinase cardiac isoenzymes in serum by batch fractionation. Clin Chem 22:92-97, Jan 1976
20. Nealon DA, Henderson AR: Separation of creatine kinase isoenzymes in serum by ion-exchange column chromatography. Clin Chem 21:392-397, Mar 1975
21. Roe CR, Limbird LE, Wagner GS, et al: Combined isoenzyme analysis in the diagnosis of myocardial injury—Application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. J Lab Clin Med 80:577-590, Oct 1972
22. Ehsani A, Ewy GA, Sobel BE: Effects of electrical countershock in serum creatine phosphokinase (CPK) isoenzyme activity. Am J Cardiol 37:12-18, Jan 1976
23. Rao PS, Luke JJ, Ayres SM, et al: New manual and automated method for determining activity of creatine kinase isoenzyme MB, by use of dithiothreitol—Clinical applications. Clin Chem 21:1612-1618, Oct 1975
24. Rao PS, Mueller HS: Evaluation of the chemical activation procedure (Rao's method) for the measurement of the MB isoenzyme of creatine kinase (Letter). Clin Chem 22:932-933, Jun 1976
25. Mercer DW: Creatine kinase MB isoenzyme—A comparison of the column chromatographic method with the selective activating method. Abstract #014, Clin Chem 22:1162, Jul 1976
26. Balkcom RM: Evaluation of the chemical activation procedure (Rao's method) for the measurement of the MB isoenzyme of creatine kinase (Letter), Clin Chem 22:929, Jun 1976
27. Sheehan M, Leipper K: Evaluation of the chemical activation procedure (Rao's method) for the measurement of the MB isoenzyme of creatine kinase (Letter). Clin Chem 22:929-930, Jun 1976
28. Hultman BK, Yasmineh WG: Evaluation of the chemical activation procedure. (Rao's method) for the measurement of the MB isoenzyme of creatine kinase (Letter). Clin Chem 22:930-931, Jun 1976
29. Muschenheim F: Evaluation of the chemical activation procedure (Rao's method) for the measurement of the MB isoenzyme of creatine kinase (Letter). Clin Chem 22:931-932, Jun 1976
30. Miyada DS, Dinovo EC, Nakamura RM: Creatine kinase reactivation by thiol compounds. Clin Chim Acta 58:97-99, Jan 20, 1975
31. Jockers-Wretou E, Pfleiderer G: Quantitation of creatine kinase isoenzymes in human tissues and sera by an immunological method. Clin Chim Acta 58:223-232, Feb 8, 1975
32. Vesell ES: Medical uses of isoenzymes, *In* Markert CL (Ed): Isoenzymes, Vol II. New York, Academic Press, 1975, pp 1-28
33. Eppenberger HM, Eppenberger M, Richerich R, et al: The ontogeny of creatine kinase isoenzymes. Develop Biol 10:1-16, Aug 1964
34. Turner DC, Eppenberger HM: Developmental changes in creatine kinase with aldolase isoenzymes and their possible function in association with contractile elements. Enzyme 15:224-238, 1973
35. Goto I, Nagamine M, Karsuki S: Creatine phosphokinase isoenzymes in muscles—Human fetus and patients. Arch Neurol 20:422-429, Apr 1969
36. Kloosterboer HJ, Stoker-de-Vries SA, Hommes FA: The development of creatine kinase in rat skeletal muscle—Changes in isoenzyme ratio, protein, RNA, and DNA during development. Enzyme 21:448-458, 1976
37. Konttinen A, Somer H: Determination of creatine kinase isoenzymes in myocardial infarction. Am J Cardiol 29:817-820, Jun 1972
38. Roberts R, Gowda KS, Ludbrook PA, et al: Specificity of elevated serum MB creatine phosphokinase activity in the diagnosis of acute myocardial infarction. Am J Cardiol 36:433-437, Oct 6, 1975
39. Roberts R, Sobel BE: Elevated plasma MB creatine phosphokinase activity. Arch Intern Med 136:421-424, Apr 1976
40. Wong R, Swallen TO: Cellulose acetate electrophoresis of creatine phosphokinase isoenzymes in the diagnosis of myocardial infarction. Am J Clin Path 64:209-216, Aug 1975
41. Yasmineh WG, Hansen NQ: Electrophoresis on cellulose acetate and chromatography on DEAE-Sephadex A-50 compared in the estimation of creatine kinase isoenzymes. Clin Chem 21: 381-386, Mar 1975
42. Klein MS, Shell WE, Sobel BE: Serum creatine phosphokinase (CPK) isoenzymes after intramuscular injections, surgery, and myocardial infarction—Experimental and clinical studies. Cardiovas Res 7:412-418, May 1973
43. Galen RS, Gambino SR: Isoenzymes of CPK and LDH in myocardial infarction and certain other diseases. Pathobiol Ann 5:283-315, 1975
44. Griffiths PD: Serum enzymes in diseases of the thyroid gland. J Clin Path 18:660-663, Sep 1965
45. Wagner GS, Roe CR, Limbird LE, et al: The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. Circulation 47:263-269, Feb 1973

46. Mercer DW: Separation of tissue and serum creatine kinase isoenzymes by ion-exchange column chromatography. Clin Chem 20:36-40, Jan 1974

47. Brownlow K, Elevitch FR: Serum creatine phosphokinase isoenzyme (CPK_2) in myositis. JAMA 230:1141-1144, Nov 25, 1974

48. Dawson DM, Fine IH: Creatine kinase in human tissues. Arch Neurol 16:175-180, Feb 1967

49. Smith AS: Separation of tissue and serum creatine isoenzymes on polyacrylamide gel slabs. Clin Chim Acta 39:351-359, Jul 1972

50. Eppenberger HM, Dawson DM, Kaplan NO: The comparative enzymology of creatine kinases—I. Isolation and characterization from chicken and rabbit tissues—II. Physical and chemical properties. J Biol Chem 242:204-209; 210-217, Jan 25, 1967

51. Eppenberger HM: Comparative aspects of the multiple forms of creatine kinase, *In* van Thoai J, Roche J (Eds): Homologous Enzymes and Biochemical Evolution. New York, Gordon and Breach, 1968, pp 231-242

52. Van der Veen KJ, Willebrands AF: Isoenzymes of creatine phosphokinase in normal and pathological sera. Clin Chim Acta 13:312-316, Mar 1966

53. Yasmineh WG, Pyle RB, Hanson NQ, et al: Creatine kinase isoenzymes in baboon tissues and organs. Clin Chem 22:63-66, Jan 1976

54. Jarmakani JM, Limbord L, Graham TC, et al: Effect of reperfusion on myocardial infarct and accuracy of estimating infarct size from serum creatine phosphokinase in the dog. Cardiovasc Res 10:245-253, Mar 1976.

55. Roberts R, Ludbrook PA, Weiss ES, et al: Serum CPK isoenzymes after cardiac catheterization. Br Heart J 37:1144-1149, Nov 1975

56. Lederer WH, Gersbrein HL, McClintock WC: A column chromatographic method for the combined analysis of creatine kinase-MB (CPK-MB) and lactate dehydrogenase 1,2 (LDH 1,2) isoenzymes. Am J Clin Path 66:425-431, Apr 1976

57. Blomberg DJ, Kimber WD, Burke MD: Creatine kinase isoenzymes—Predictive value in the early diagnosis of acute myocardial infarction. Am J Med 59:464-469, Oct 1975

58. Smith AF, Radford D, Wong CP, et al: Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. Br Heart J 38:225-232, Mar 1976

59. Galen RS: The enzyme diagnosis of myocardial infarction. Human Path 6:141-155, Mar 1975

60. Nevins MA, Saran M, Bright M, et al: Pitfalls in interpreting serum creatine phosphokinase activity. JAMA 224:1382-1387, Jun 4, 1973

61. Galen RS, Reiffel JA, Gambino R: Diagnosis of acute myocardial infarction—Relative efficiency of serum enzyme and isoenzyme measurements. JAMA 232:145-147, Apr 14, 1975

62. King SW, Statland BE, Savory J: The effect of a short burst of exercise on activity of enzymes in sera of healthy young men. Clin Chim Acta 72:211-218, Oct 15, 1976

63. Oldham HN, Roe CR, Young WG, et al: Intraoperative detection of myocardial damage during coronary artery surgery by plasma creatine phosphokinase isoenzyme analysis. Surgery 74:917-925, Dec 1973

64. Dixon SS, Limbird LE, Roe CR, et al: Recognition of postoperative acute myocardial infarction—Application of isoenzyme techniques. Circulation 47&48(Supplement III):137-140, Jul 1973

65. Pyle RB, Blomberg DJ, Burke MD, et al: CPK-MB isoenzyme—Use on diagnosis of acute myocardial infarction in the early post-operative period. J Thorac Cardiovasc Surg 71:884-890, Jun 1976

66. Codd JE, Kaiser GC, Wiens RD, et al: Myocardial injury and bypass grafting—Value of serum enzymes in diagnosis. J Thorac Cardiovasc Surg 70:489-494, Sep 1975

67. Assad-Morell JL, Wallace RB, Elveback LR, et al: Serum enzyme data in diagnosis of myocardial infarction during or early after aorta-coronary saphenous vein bypass graft operations. J Thorac Cardiovasc Surg 69:851-857, Jun 1975

68. Mohuiddin SM, Raffetto J, Sketch HM, et al: LDH isoenzymes and myocardial infarction in patients undergoing coronary bypass surgery—An excellent correlation. Am Heart J 92:584-588, Nov 1976

69. Klein MS, Coleman RE, Weldon CS, et al: Concordance of electrocardiographic and scintigraphic criteria of myocardial injury after cardiac surgery. J Thorac Cardiovasc Surg 71:934-937, Jun 1976

70. Bassan MM, Oatfield R, Hoffman I, et al: New Q waves after aortocoronary bypass surgery—Unmasking of an old infarction. N Engl Med 290:349-353, Feb 14, 1974

71. Helfant RH: Q waves in coronary heart disease—New understanding of their clinical implications. Am J Cardiol 38:662-664, Nov 4, 1976

72. Coleman RE, Klein MS, Roberts R, et al: Improved detection of myocardial infarction with technetium-99m stannous pyrophosphate and serum MB creatine phosphokinase. Am J Cardiol 37:732-735, Apr 1976

73. Soin JS, Burdine A, Beal W: Myocardial localization of 99m Tc-pyrophosphate without evidence of myocardial infarction. J Nuc Med 16:944-946, Oct 1975

74. Perez LA: Clinical experience—Technetium-99m labeled phosphates in myocardial imaging. Clin Nuc Med 1:2-9, Jun 1976

75. Varat MA, Mercer DW: Cardiac specific creatine phosphokinase isoenzymes in the diagnosis of acute myocardial infarction. Circulation 51:855-859, May 1975

76. Galen RS, Gambino SR: Creatine kinase isoenzyme MB and heart disease. Clin Chem 21:1848-1849, Nov 1975

77. Mercer DW, Varat MA: Detection of cardiac-specific creatine kinase in sera with normal or slightly increased total creatine kinase activity. Clin Chem 21:1088-1092, July 1975

78. Tonkin AM, Lester RM, Guthrow CE, et al: Persistence of MB isoenzyme of creatine phosphokinase in the serum after minor iatrogenic cardiac trauma—Absence of postmortem evidence of myocardial infarction. Circulation 51:627-631, Apr 1975

79. Silverman LM, Mandell JR, Gruemer HD: Creatine kinase isoenzymes in muscular dystrophy. Abstract #058, Clin Chem 20:865, Jul 1974

80. Anido V, Conn RB, Mengoli HF, et al: Diagnostic efficacy of myocardial creatine phosphokinase using polyacrylamide disc gel electrophoresis. Am J Clin Path 61:599-605, May 1974

81. Doran GR, Wilkinson JH: The origin of the elevated activities of creatine kinase and other enzymes in the sera of patients with myxoedema. Clin Chim Acta 62:203-211, Jul 23, 1975

82. Roberts R, Sobel BE: Isoenzymes of creatine phosphokinase and diagnosis of myocardial infarction (Editorial). Ann Intern Med 79:741-743, Nov 1973

83. Konttinen A, Somer H: Specificity of serum creatine kinase isoenzymes in diagnosis of acute myocardial infarction. Br Med J 1:386-389, Feb 17, 1973

84. Goto I: Serum creatine phosphokinase isoenzymes in hypothyroidism, convulsion, myocardial infarction and other diseases. Clin Chim Acta 52:27-30, Apr 11, 1974

85. Galen RS: Creatine kinase isoenzyme BB in serum of renal disease patients. Letter, Clin Chem 22:120, Jan 1976

86. Lederer WH, Gerstbrein HL: Creatine kinase isoenzyme BB activity in serum of a patient with gastric cancer. Clin Chem 22:1748-1749, Oct 1976

87. Zsigmond EK, Starkweather WH, Duboff GS, et al: Abnormal creatine-phosphokinase isoenzyme pattern in families with malignant hyperpyrexia. Anesth Analg (Cleve) 51:827-837, Sep-Oct 1972

88. Itano M: The detection of CPK_1 (BB) in serum—A summary of sixteen cases. Am J Clin Path 65:351-355, Mar 1976

89. Coolen RB, Pragay DA, Chilcote ME: The occurrence of the brain (BB) isoenzyme of serum creatine kinase (CK) in different diseases as determined by quantitative electrophoresis and ion exchange column chromatography. Abstract #183, Clin Chem 21:976, Jun 1975

90. Nealon DA, Henderson AR: Measurement of brain-specific creatine kinase isoenzyme activity in serum. Clin Chem 21:1663-1666, Oct 1975

91. Bayer PM, Gabl F, Granditisch G, et al: Creatine kinase isoenzymes in CSF in a case of brain damage. Clin Chem 22: 1405-1407, Aug 1976

92. Somer H, Kaste M, Troupp H, et al: Brain creatine kinase in blood after acute brain injury. J Neurol Neurosurg Psych 38: 572-576, June 1975

93. Shell WE, Sobel BE: Biochemical markers of ischemic injury. Circulation 53(Supplement I):98-106, Mar 1976

94. Shell WE, Kjekshus JK, Sobel BE: Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in creatine phosphokinase activity. J Clin Invest 50:2614-2625, Dec 1971

95. Althaus U, Janett J, Scholl E, et al: Effects of myocardial revascularization following acute coronary occlusion in pigs. Europ J Clin Invest 6:7-16, Feb 1976

96. Ahumada G, Roberts R, Sobel BE: Evaluation of myocardial infarction with enzymatic indices. Prog Cardiovas Diseases 18:405-420, Mar-Apr 1976

97. Mathey D, Bleifeld W, Buss H, et al: Creatine kinase release in acute myocardial infarction—Correlation with clinical, electrocardiographic, and pathological findings. Br Heart J 37:1161-1168, Nov 1975

98. Norris RM, Whitlock RML, Barratt-Bayes C, et al: Clinical measurement of myocardial infarct size—Modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction. Circulation 51:614-620, Apr 1975

99. Roberts R, Henry PD, Sobel BE: An improved basis for enzymatic estimation of infarct size. Circulation 52:743-754, Nov 1975

100. Ahmed SA, Williamson JR, Roberts R, et al: The association of increased plasma MB-CPK activity and irreversible ischemic myocardial injury in the dog. Circulation 54:187-193, Aug 1976

101. Kjekshus JK, Sobel BE: Depressed myocardial CPK activity following experimental myocardial infarction in rabbit. Circulation Res 27:403-414, Sep 1970

102. Baba N, Kim S, Farrell EC: Histochemistry of creatine phosphokinase J Mol Cell Cardiol 8:599-617, Jul 1976

103. Roe CR, Starmer CF: A sensitivity analysis of enzymatic estimation of infarct size. Circulation 52:1-5, Jul 1975

104. Rapaport E: The fractional disappearance rate of the separate isoenzymes of creatine phosphokinase in the dog. Cardiovasc Res 9:473-477, Jul 1975

105. Sunderman FW: Current concepts of "normal values," "reference values," and "discrimination values" in clinical chemistry. Clin Chem 21:1873-1877, Dec 1975

106. Galen RS, Gambino SR: Beyond Normality—The Predictive Value and Efficiency of Medical Diagnosis. New York, John Wiley and Sons, 1975